Ethical and Regulatory Aspects of Clinical Research

NIH CC Department of Bioethics

Wednesdays, September 22- November 3, 2010

Course Readings

Readings are listed under each topic below. The list has been divided into readings that you should read for each session and some additional recommendations. The readings will be found either in the following course textbook (those listed by chapter) or on the supplemental course CD provided. *Please note the instruction after each citation for the location of the readings on the CD.*

Course Textbook:

Emanuel E, R. Crouch, J. Arras, J. Moreno, and C. Grady. Ethical and Regulatory Aspects of Clinical Research: Readings and Commentary. Baltimore: Johns Hopkins University Press 2003. (Available from the FAES bookstore)

September 22, 2010 **Session 1: History, Guidance, and Framework for Ethical Clinical Research**

8:30-8:40 Pre-test

8:40-9:20 **Intro and Framework for the Ethics of Research with Human Subjects**
Christine Grady RN PhD
NIH Clinical Center Dept of Bioethics

9:20-9:30 **Discussion**

9:30- 10:15 **History, Scandals and Tragedies: Beecher, Tuskegee, Willowbrook and the Rest**
Susan E. Lederer Ph.D.
University of Wisconsin

10:15- 10:25 **Discussion**

Chapter 4. Brandt, A.. "Racism and Research: The case of the Tuskegee Syphilis Study.".

10:25-10:40 **Break**

10:40-11:20 **Do the Codes Apply to My Research? Nuremberg, Helsinki, the Belmont Report, CIOMS, and the Common Rule**
Heidi Gertner JD
FDA Office of the General Counsel

11:20-11:30 Discussion

Readings for Session 1:

Emanuel E, Wendler D, Grady C. What makes Clinical Research Ethical? *JAMA* 2000; 283 (20): 2701-2711 *(**N.B.** found on the CD under session 1)*

Textbook: Intro to Part 1 and II

Chapter 3. Beecher, H. "Ethics and clinical research."

Recommended supplementary readings for session 1:

Chapter 1. Faden et al. "US medical researchers, the Nuremberg Doctors Trial, and the Nuremberg Code."

Chapter 2. Katz et al. "The Jewish chronic disease case,"

Chapter 4. Brandt, A. "Racism and Research: The case of the Tuskegee Syphilis Study.".

Chapter 5. The Nuremberg Code

Chapter 6. The Declaration of Helsinki

Chapter 7. The Belmont Report

Chapter 8. The Common Rule

PLEASE READ THE PROTOCOL *THAT IS ON THE CD IN PREPARATION FOR THE IRB DISCUSSION ON 9/29. TO FIND IT- OPEN THE CD, CLICK ON SESSION **3**, AND CLICK ON VRC 206 PROTOCOL MODIFIED FOR TEACHING*

Sept. 29, 2010 Session 2: IRB review, Conflicts of Interest and Investigator perspectives

8:30-9:15 Purpose and Function of IRBs: Successes and Current Challenges
Barbara Karp MD
Chair of CNS and NIDA IRBs/NIH

9:15-9:25 Discussion

9:25-10:10 Conflicts of Interest
Steve Joffe MD MPH
Dana Farber Cancer Institute

1**0:10-10:20 Discussion**

10:20-10:35 Break

10:35-11:30 Mock IRB

Readings for Session 2

Chapter 8. The Common Rule

Chapter 72. Thompson D. "Understanding Financial Conflicts of Interest"

Recommended supplementary readings for Session 2

Chapter 74. Brody B. Conflicts of Interest and the Validity of Clinical trials.
Chapter 75. Martin, JB and Kasper, DL. "In whose best interest? Breaching the academic-industrial wall."
Chapter 85. Edgar H, Rothman D. "The Institutional Review Board and Beyond: Future challenges to the ethics of human experimentation."

CD (*(**N.B.** found on the CD under session 2)*
Emanuel E, et al. Oversight of Human Participants Research: Identifying Problems to Evaluate Reform Proposals. *Annals of Internal Medicine* 2004; 141(4):282-291
Beckelman J, Li Y, Gross C. Scope and Impact of Financial Conflicts of Interest in Biomedical Research. *JAMA* 2003; 289: 464-465.
Bodenheimer, T. "Uneasy alliance. Clinical investigators and the pharmaceutical industry." *NEJM;* 2000; 342(20):1539-1544.
Hampson LA, et al. Patients's views on financial conflicts of interest in Research trials. *NEJM* 2006; 355:
Krumholz HM et al. What have we learnt from Vioxx? *BMJ* 2007; 334:120-123
Lexchin J, Bero L, Djulbegovic B, Clark O. Pharmaceutical industry sponsorship and research outcome and quality: systematic review**.** *BMJ* 2003; 326: 1167-1170

October 6, 2010 **Session 3: Randomized Clinical Trials, the use of placebo, and research with stored tissue and data**

8:30-9:15 **Ethics of Randomized Clinical Trials: Clinical Equipoise**
Robert Truog, M.D.
Professor of Anesthesiology & Medical Ethics
Harvard Medical School

9:15-9:25 **Discussion**

9:25- 10:10 **Ethics of Placebo Controlled Trials**
Frank Miller, Ph.D.
Department of Bioethics CC/NIH

10:10- 10:20 **Discussion**

10:20- 10:40 **Break**

10:40-11:20 **Ethical Issues in the Use of Stored Tissue and Data**
Sara Chandros Hull, Ph.D.
NHGRI and Dept of Bioethics

11:20- 11:30 **Discussion**

Readings for Session 3

Textbook
Part III, Intro Sections 1, 2, 3
Chapter 14. Freedman B. "Equipoise and the ethics of clinical research."

Chapter 15. Truog R. “Randomized Controlled Trials: Lessons from ECMO
Chapter 17. Freedman B. “Placebo-Controlled trials and the logic of clinical purpose”
Chapter 19. Emanuel EJ, Miller FG. “The Ethics of Placebo-Controlled Trials – A Middle Ground.”

Recommended supplementary readings for Session 3:

Chapter 11. Levine R. "Research and practice,"
Chapter 13. Hellman S, & Hellman DS. “Of mice but not men: Problems of the randomized clinical trial.”
Chapter 16. Rothman K, Michels K. “The continuing unethical use of placebo controls.”
Chapter 18. Temple R, Ellenberg S. “Placebo-Controlled Trials and Active-Control Trials in the Evaluation of New Treatments, Part 1: Ethical and Scientific Issues.”
Chapter 53. Wright, E, et al. “Informed consent for genetic research on stored tissue samples.”
Chapter 54. Merz, J et al. “Use of human tissues in research: Clarifying clinician and researcher roles and information flows

CD ***(N.B. these 2 articles can be found under session 5 on the CD)***
National Bioethics Advisory Commission. “Research Involving Human Biological Materials: Ethical Issues and Policy Guidance – Executive Summary,” August 1999**.**
Caulfield T, McGuire A, Cho M et al. Research ethics recommendations for whole genome research: Consensus Statement. *PLoS Biology* 2008; 6(3):e73

October 13, 2010 **Session 4: Selection and recruitment of research participants**

8:30-9:15 **Fair Subject Selection**
Dave Wendler PhD
NIH Clinical Center Dept of Bioethics

9:15-9:25 **Discussion**

9:25- 10:10 **Recruitment, Undue influence and Coercion**
Alan Wertheimer, Ph.D.
NIH Clinical Center Dept of Bioethics

10:10- 10:20 **Discussion**

10:20- 10:35 **Break**

10:35- 11:30 **Investigator panel**

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Readings for Session 4:
Chapter 27, Dickert N, Grady C. “What’s the price of a research subject”?
Wendler D. When should ‘riskier’ subjects be excluded from research? *Kennedy Institute of Ethics Journal* 1998; 8:307-327. ***(N.B.** found on the CD under session 2)*
Emanuel, EJ. Ending Concerns about Undue Inducement. *Journal of Law, Medicine & Ethics* 2004;32:100-105. ***(N.B.** found on the CD under session 3)*

Recommended supplementary readings for Session 4

Textbook
Chapter 28, Lemmens T, Elliott C. "Justice for the professional guinea pig"
Chapter 29, McNeill P. "Paying people to participate: why not?"
Supplementary readings on CD
Emanuel, EJ. Undue Inducement – Nonsense on Stilts. *American Journal of Bioethics* 2005;5(5):9-13. *(**N.B.** found on the CD under session 3)*

October 20, 2010 **Session 5: Risks and Benefits and research with children**

8:30-9:15 **Assessment of Risks and Benefits**
Dave Wendler PhD
NIH Clinical Center Dept of Bioethics

9:15-9:25 **Discussion**

9:25-10:10 **Ethical issues in research with children**
Robert Nelson MD PhD
FDA

10:10-10:20 **Discussion**

10:20-10:35 **Break**

10:35- 11:30 **Participant perspectives**

Readings for Session 5:
King N, Defining and Describing Benefit Appropriately in Clinical Trials
J Law Med Ethics 2000; 28:332-43 *(**N.B.** found on the CD under session 5)*
Chapter 42. Freedman B, Fuks A, Weijer C. "*In loco parentis*: Minimal risk as an ethical threshold for research upon children,"

Recommended supplementary readings for session 5:
Chapter 41. Tauer C. "The NIH trials of growth hormone for short stature."
Chapter 43. Leikin S. "Minors assent, consent, or dissent to medical research."
Weijer C & Miller PB When Are Research Risks Reasonable in Relation to Anticipated Benefits? *Nature Medicine* 2004;10(6):570-3 *(**N.B.** found on the CD under session 5)*
D Wendler. Is it Possible to Protect Pediatric Research Subjects without Blocking Appropriate Research? J Pediatr. 2008 Apr;152 (4):467-70 *(**N.B.** found on the CD under session 5)*

October 27, 2010 **Session 6: Ethics of international research**

8:30-9:15 **Exploitation and standard of care**
Alan Wertheimer PhD
NIH Clinical Center Dept of Bioethics

9:15-9:25 **Discussion**

9:25- 10:10 **International research**
Seema Shah

10:10- 10:20 **Discussion**

10:20- 10:35 **Break**

10:35- 11:30 Case discussion
Joe Millum

Readings for Session 6

Chapter 65. Lurie P & Wolfe S. "Unethical Trials of Interventions to Reduce Perinatal Transmission of the Human Immunodeficiency Virus in Developing Countries"
Chapter 68. Participants in the 2001 conference on Ethical Aspects of Research in Developing Countries**.** Fair benefits for Research in Developing countries.

Wertheimer A. Exploitation**.** Chapter 20 in E. Emanuel et al (eds). *The Oxford Textbook of Clinical Research Ethics*. New York: Oxford University Press, 2008, pages 201-210
***(N.B.** found on the CD under session 7)*

Emanuel E, Wendler D, Killen J, Grady C. What Makes Clinical Research in Developing Countries Ethical? The Benchmarks of Ethical Research *J Inf Dis* 2004; 189:930-7.
***(N.B.** found on the CD under session 7)*

Recommended Supplementary Readings for session 6:

Chapter 66. Annas G & Grodin M. "Human Rights and Maternal-Fetal HIV Transmission Prevention Trials in Africa"

November 3, 2010 **Session 7: informed consent and special populations**

8:30- 9:15 **Informed Consent**
Christine Grady RN PhD
NIH Clinical Center Department of Bioethics

9:15- 9:25 **Discussion**

9:25- 10:10 **Research Involving Persons at Risk for Impaired Decision-Making**
Don Rosenstein, M.D.
University of North Carolina Medical Center

10:05-10:15 **Discussion**

10:15- 10:30 **Break**

10:30-11:10 **Clinical Research with pregnant women**

Maggie Little PhD
Georgetown University

11:10- 11:20 Discussion

11:20- 11:30 Post tests and evaluations

Readings for Session 7:

Chapter 24. Dresser, R. Wanted: Single, White Male for Medical Research
Chapter 25. Weijer, C and Crouch R. Why Should We Include Women and Minorities in Randomized Controlled Trials.
Chapter 32 Freedman, B. A moral theory of informed consent
Chapter 38. National Bioethics Advisory Commission, excerpts from "Research Involving Persons with Mental Disorders That May Affect Decision-making Capacity"

Flory J, Emanuel E. Interventions to improve research participants' understanding in informed consent for research: a systematic review. *JAMA*. 2004 Oct 6;292(13):1593-601. ***(N.B.** found on the CD under session 4)*
Chen DT, Miller FG, Rosenstein DL. "Enrolling Decisionally Impaired Adults in Clinical Research." *Medical Care*, 2002, Vol. 40(9) 20-29**.** ***(N.B.** found on the CD under session 4)*

Recommended Supplementary readings for session 7:

Chapter 31 Inglefinger, F. Informed (but uneducated) consent
Chapter 33. Truog R, et al. Is Informed Consent Always Necessary for Randomized, Controlled Trials?
Chapter 36. Appelbaum P, Roth L., Lidz C, et al. "False hopes and best data: Consent to research and the therapeutic misconception."
Kim Scott YH, Karlawish Jason HT, Caine Eric D. "Current State of Research on Decision-Making Competence of Cognitively Impaired Elderly Persons." *Am J Geriatric Psychiatry*, 2002; 10(2):151-165**.** ***(N.B.** found on the CD under session 4)*
Misra S, Ganzini L. Capacity to consent to research among patients with bipolar disorder. *Journal of Affective Disorders*. 2004; 80:115-123 ***(N.B.** found on the CD under session 4)*
Dan Brock, "Philosophical Justifications of Informed Consent in Research," *Oxford Textbook* ***(N.B.** found on the CD under session 4)*
Sreenivasan G. Does Informed Consent to Research Require Comprehension? *Lancet* 2003;362:2016-8 ***(N.B.** found on the CD under session 4)*
Sachs GA, Hougham GW, Sugarman J, Agre P, Broome ME, Geller G, Kass N, Kodish E, Mintz J, Roberts LW, Sankar P, Siminoff LA, Sorenson J, Weiss A. Conducting empirical research on informed consent: challenges and questions. *IRB*. 2003 Sep-Oct; Suppl 25(5):S4-**S10.** ***(N.B.** found on the CD under session 4)*